Ritonavir-boosted darunavir combined with raltegravir or tenofovir–emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial

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Summary

Background Standard first-line antiretroviral therapy for HIV-1 infection includes two nucleoside or nucleotide reverse transcriptase inhibitors (NtRTIs), but these drugs have limitations. We assessed the 96 week efficacy and safety of an NtRTI-sparing regimen.

Methods Between August, 2010, and September, 2011, we enrolled treatment-naive adults into this randomised, open-label, non-inferiority trial in treatment-naive adults in 15 European countries. The composite primary outcome was change to randomised treatment before week 32 because of insufficient virological response, no virological response by week 32, HIV-1 RNA concentration 50 copies per mL or higher at any time after week 32; death from any cause; any new or recurrent AIDS event; or any serious non-AIDS event. Patients were randomised in a 1:1 ratio to receive oral treatment with 400 mg raltegravir twice daily plus 800 mg darunavir and 100 mg ritonavir once daily (NtRTI-sparing regimen) or tenofovir–emtricitabine in a 245 mg and 200 mg fixed-dose combination once daily, plus 800 mg darunavir and 100 mg ritonavir once daily (standard regimen). This trial was registered with ClinicalTrials.gov, number NCT01066962.

Findings Of 805 patients enrolled, 401 received the NtRTI-sparing regimen and 404 the standard regimen, with median follow-up of 123 weeks (IQR 112–133). Treatment failure was seen in 77 (19%) in the NtRTI-sparing group and 61 (15%) in the standard group. Kaplan-Meier estimated proportions of treatment failure by week 96 were 17·8% and 13·8%, respectively (difference 4·0%, 95% CI –0·8 to 8·8). The frequency of serious or treatment-modifying adverse events were similar (10·2 *vs* 8·3 per 100 person-years and 3·9 *vs* 4·2 per 100 person-years, respectively).

Interpretation Our NtRTI-sparing regimen was non-inferior to standard treatment and represents a treatment option for patients with CD4 cell counts higher than 200 cells per µL.

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Introduction

The recommended initial therapy for infection with HIV-1 in Europe is combination antiretroviral therapy that includes two nucleoside or nucleotide analogue reverse transcriptase inhibitors (NtRTIs) and a non-nucleoside reverse transcriptase inhibitor, a ritonavir-boosted protease inhibitor, or an integrase strand-transfer inhibitor.[1] Despite being recommended for all first-line regimens, the tolerability and toxicity profiles of NtRTIs are limiting. For instance, the fixed-dose combination of tenofovir and emtricitabine, which is the cornerstone of initial therapy, is associated with renal and bone complications.[2–4] These drawbacks have led to the investigation of alternative combinations that do not contain NtRTIs to expand treatment options. So far, no NtRTI-sparing first-line regimen has shown satisfactory efficacy and safety profiles in a fully powered phase 3 trial.

Darunavir is a drug with potent antiviral activity and a favourable safety profile.[5,6] First-line treatment with raltegravir, the first-approved inhibitor of integrase strand transfer, results in a rapid reduction of HIV viral load when given in combination with other antiretrovirals[7,8] and has no expected clinically relevant pharmacokinetic interaction with ritonavir-boosted darunavir.[9] A regimen of raltegravir plus ritonavir-boosted darunavir combines two potent antiretrovirals, each of which has demonstrated tolerability and durable antiviral efficacy, and avoids toxic effects associated with NtRTIs. This treatment could, therefore, represent an alternative option for the initial treatment of adults infected with HIV-1.

We did a randomised phase 3 strategic trial to compare the NtRTI-sparing regimen of raltegravir and ritonavir-boosted darunavir with one of the recommended standard three drug regimens, tenofovir–emtricitabine plus ritonavir-boosted darunavir in treatment-naive

adults. We hypothesised that the NtRTI-sparing strategy would have non-inferior efficacy to and a better safety profile than the standard regimen.

Methods

Study design and patients

NEAT001/ANRS143 was a randomised, open-label, non-inferiority trial done in 78 clinical sites in 15 European countries (appendix p 1) between August, 2010, and October, 2013. Patients were recruited between August, 2010, and September, 2011. Eligible patients had plasma viral loads higher than 1000 HIV RNA copies per mL and no evidence of major International Antiviral Society-USA resistance mutations[10] on genotype testing, historically or at screening. Participants had to have CD4 cell counts of less than 500 cells per μL, except in those with symptomatic HIV infection, in line with the European recommendations for starting treatment.[11] Patients were excluded if they were receiving treatment for mycobacteriosis or malignant disease, tested positive for HBsAg, were pregnant or had relevant abnormal laboratory results or medical characteristics, including moderate to severe hepatic impairment, an anticipated need for hepatitis C treatment during the first year of the trial, and an estimated creatinine clearance less than 60 mL/min. The eligibility criteria were selected to enrol a study population similar to that in the trial that established the efficacy of the standard regimen tenofovir–emtricitabine plus ritonavir-boosted darunavir.[12]

Ethics committee approval was obtained from all participating centres, in accordance with the principles of the Declaration of Helsinki. All trial participants gave written informed consent.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive oral treatment with 400 mg raltegravir twice daily plus 800 mg darunavir and 100 mg ritonavir once daily (NtRTI-sparing regimen) or tenofovir–emtricitabine in a 245 mg and 200 mg fixed dose combination once daily, plus 800 mg darunavir and 100 mg ritonavir once daily (standard regimen). In both regimens darunavir was administered as two 400 mg tablets.[12]

The randomisation list was generated by the trial statistician before the start of the study, who used permuted blocks of randomly varying sizes, and was stratified by country and prespecified participation in the viral and immunological dynamics and inflammation substudy. A central, secure, web-based randomisation tool enabled staff at the clinical trial units to randomise patients at the baseline visit. Allocation was masked until randomisation, after which treatment was open label, but only the trial statistician had access to the entire randomisation list during the trial.

Study procedures

Patients attended study centres at screening, baseline, weeks 2, 4, 8, 12, 18, 24, 32, 48, 64, 80, and 96, and every 12–16 weeks thereafter. All patients remained in the study until the last patient enrolled had completed the week 96 visit. Each visit included assessment of vital signs and adverse events, physical examination, and collection of blood samples for full blood cell counts and serum chemistry, liver function and immunovirological measurements. CD4 cell counts and viral loads in plasma were measured at all visits except week 2. Fasting lipid and glucose concentrations in serum were measured at all visits except weeks 18, 32, 64, and 80. Glomerular filtration rate was estimated by the Cockcroft-Gault formula.[13] HIV RNA measurements in plasma and testing for antiretroviral resistance by genotype sequencing were done at local laboratories with commercially available viral load assays and standardised genotypic resistance tests, with no change in the kits throughout the trial. Genotypic analysis was done at screening and at all visits from 32 weeks onwards for patients who had HIV-1 RNA concentrations

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See **Online** for appendix

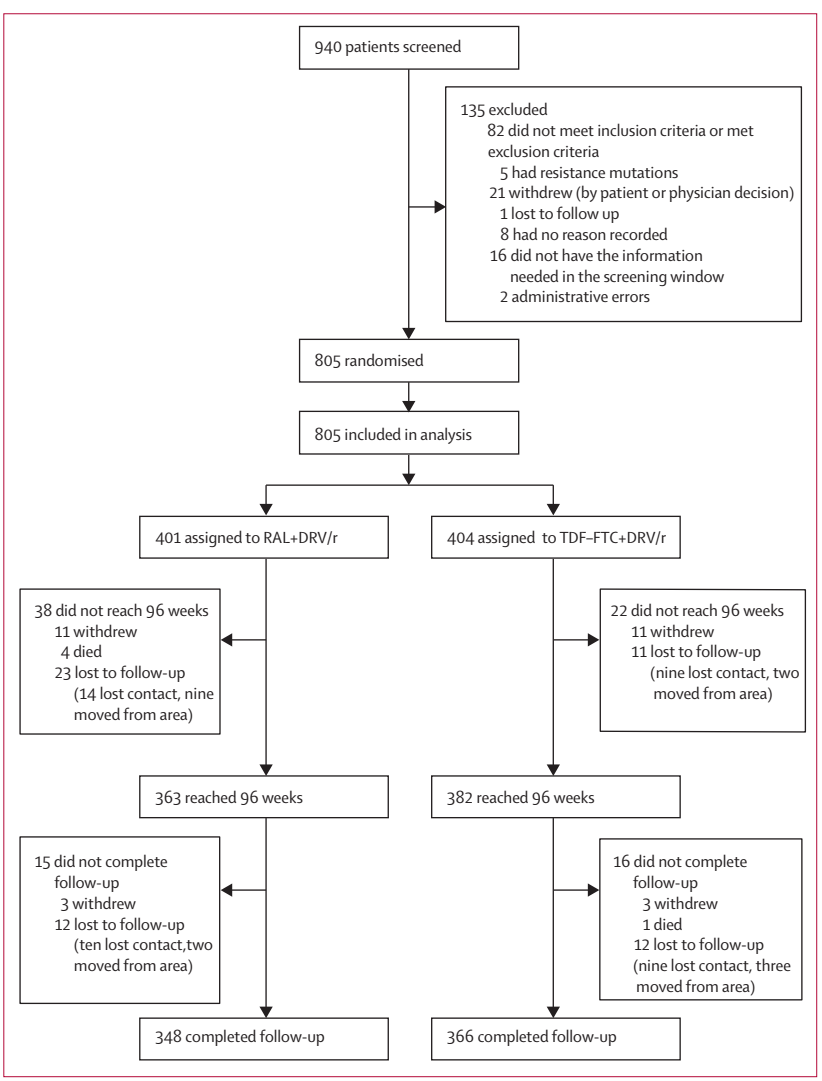

***Figure 1*: Trial profile**
RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine.

	RAL+DRV/r (n=401)	TDF–FTC+DRV/r (n=404)
Sex		
Male	352 (88%)	358 (89%)
Median (IQR) age (years)	37 (31–45)	39 (31–46)
Ethnic origin		
White	328 (82%)	330 (82%)
Black	54 (13%)	47 (12%)
Asian	9 (2%)	10 (2%)
Other	10 (3%)	17 (4%)
Mode of HIV infection*		
Homosexual/bisexual sex	272 (72%)	279 (72%)
Heterosexual sex	97 (26%)	98 (25%)
Intravenous drug use	9 (2%)	11 (3%)
Blood or blood product receipt	1 (<1%)	0
Other	3 (1%)	4 (1%)
HIV CDC clinical stage		
A	334 (83%)	332 (82%)
B	48 (12%)	53 (13%)
C	19 (5%)	19 (5%)
Median (IQR) CD4 cell count (cells per µL)	340 (260–394)	325 (248–401)
CD4 cell count category (cells per µL)		
<50	11 (3%)	18 (5%)
50–199	49 (12%)	45 (11%)
200–349	160 (40%)	173 (43%)
350–499	157 (39%)	151 (37%)
≥500	24 (6%)	17 (4%)
Median (IQR) HIV-1 RNA concentration at baseline (log_{10} copies per mL)	4·78 (4·30–5·17)	4·75 (4·32–5·12)
Baseline HIV-1 RNA category		
≥100 000 copies per mL	146 (36%)	129 (32%)
≥500 000 copies per mL	25 (6%)	21 (5%)
HCV co-infection	16 (4%)	18 (4%)

Data are number (%) unless stated otherwise. RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine. CDC=Centers for Disease Control and Prevention. HCV=hepatitis C virus. *Percentages are based only on patients with available data (RAL+DRV/r n=378, TDF-FTC+DRV/r n=389); seven patients had more than one risk factor (RAL+DRV/r n=4, TDF–FTC+DRV/r n=3).

***Table 1*: Baseline characteristics**

	RAL+DRV/r (n=401)	TDF–FTC+DRV/r (n=404)
Total patients meeting primary endpoint during follow-up	77 (19·2%)	61 (15·3%)
Changed regimen because of insufficient response		
<1 log_{10} copies per mL reduction in HIV RNA concentration at week 18	1	0
HIV RNA concentration ≥400 copies/ per mL at week 24	0	0
HIV RNA concentration ≥50 copies per mL at week 32	27	28
HIV RNA concentration ≥50 copies per mL after week 32	33	22
Death	3	1
AIDS event	5	3
Serious non-AIDS event	8	7

If a patient reached more than one component, only the first was taken into account. RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine.

***Table 2*: Patients who met the primary endpoint**

in plasma of 500 copies per mL or higher. Safety was assessed at all visits by monitoring of all adverse and serious adverse events, vital signs, and laboratory values.

Endpoints

The primary outcome was the time to virological or clinical failure, defined as the first occurrence of any of the following components: change of any component of the initial randomised regimen before week 32 because of documented insufficient virological response (defined as reductions of less than 1 log_{10} copies per mL in HIV-1 RNA by week 18 or HIV-1 RNA 400 copies per mL or higher at week 24); failure to achieve virological response by week 32 (defined as HIV-1 RNA concentrations of 50 copies per mL or higher); HIV-1 RNA concentrations of 50 copies per mL or higher at any time after week 32; death from any cause; any new or recurrent AIDS event; or any serious non-AIDS event (infection, liver cirrhosis, chronic renal disease, cardiovascular event, and non-AIDS-related malignant disease). AIDS events and serious non-AIDS events had to be confirmed by the endpoint review committee, whose members were unaware of patients' treatment groups. All virological components of the primary endpoint had to be confirmed by a second measurement after virological failure was suspected. The secondary endpoints were changes from baseline in CD4 cell count, incidence and severity of adverse events, changes in laboratory parameters, and genotypic evidence of resistance.

Statistical analyses

An upper bound of the two-sided 95% CI for the absolute difference in the proportion of participants reaching the primary endpoint by week 96 was set at 9% for the non-inferiority threshold for the NtRTI-sparing regimen. This limit was chosen by a panel of European HIV experts and approved by the trial steering committee. We assumed cumulative probability of failure of 20% in the standard regimen group, based on a previous 96-week analysis that was reanalysed to mirror our endpoint definition.[12] Thus, we calculated that a sample size of 400 assessable patients per group would be required to provide 85% power to identify non-inferiority if the two regimens were equally efficacious, at a two-sided significance level of 5%. The 9% non-inferiority margin would, therefore, correspond to a hazard ratio (HR) of 1·53 if an exponential distribution for time to the primary outcome was achieved.

The primary endpoint was assessed with the Kaplan-Meier method and adjusted for stratification factors. The two treatment groups were compared as randomised, according to the intention-to-treat principle, with censoring of observations at the first date of meeting the primary endpoint, completion of 96 weeks of follow-up, last time the primary endpoint status was known, or date of withdrawal. For patients with at least

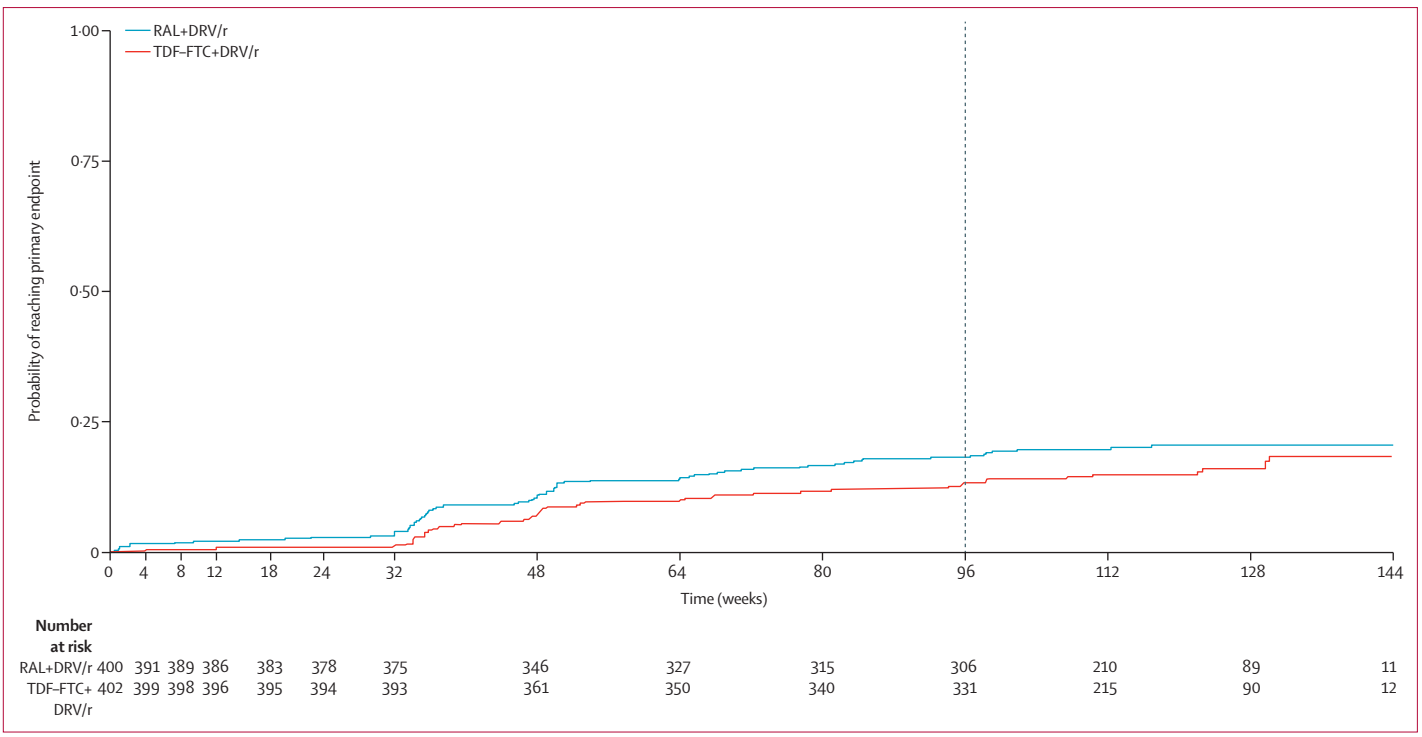

***Figure 2*: Kaplan-Meier plot of time from randomisation to primary endpoint**
RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine.

one component of the primary endpoint the results are summarised as number (%). We specified subgroup analyses of the primary endpoint by baseline CD4 cell count and HIV-1 RNA concentration. Data were analysed with Stata (version 12.1).

Prespecified secondary efficacy analyses were a per-protocol analysis, censoring of events if any component of the initial randomised trial treatment was stopped, an intention-to-treat analysis that included treatment modification as a component of failure, and an assessment of time to loss of virological response by week 48 and week 96 (defined as meeting any of the virological components of the primary outcome or change to the allocated regimen for any reason). All secondary endpoints were assessed with statistical methods testing for superiority.

An independent data monitoring committee reviewed safety and efficacy data on three occasions. The monitoring guidelines stated that the independent data monitoring committee was to inform the trial steering committee if there was either unequivocal evidence (based on the Haybittle-Peto criterion[14] of a treatment difference of at least 3 SD) that one of the two regimens was clearly clinically indicated in all or a subgroup of participants, or if there was good evidence (based on a treatment difference of at least 2 SD) that the standard regimen was superior to the NtRTI-sparing regimen in terms of the primary outcome to an extent that meant non-inferiority was unlikely to be seen with continued enrolment, follow-up, or both. The committee recommended that the study proceed without change after each review. This trial was registered with ClinicalTrials.gov, number NCT01066962.

Roles of the funding sources

The funders of the study other than Inserm-ANRS had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Inserm-ANRS had a role in study design, data collection, data analysis, data interpretation, and approval of the final report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 940 patients screened 135 were excluded (figure 1). Of the 805 enrolled, 401 were randomised to receive the NtRTI-sparing regimen and 404 to the standard regimen. Seven patients did not start the allocated regimen (one in the NtRTI-sparing group withdrew at randomisation and two started on non-randomised or non-study regimens; three in the standard group withdrew and one started on a non-study regimen). Baseline demographics and clinical characteristics were similar in the two treatment groups (table 1). Median follow-up was 123 weeks (IQR 112–133).

During follow-up, 77 (19%) patients taking the NtRTI-sparing regimen and 61 (15%) taking the standard regimen experienced treatment failure as defined by the

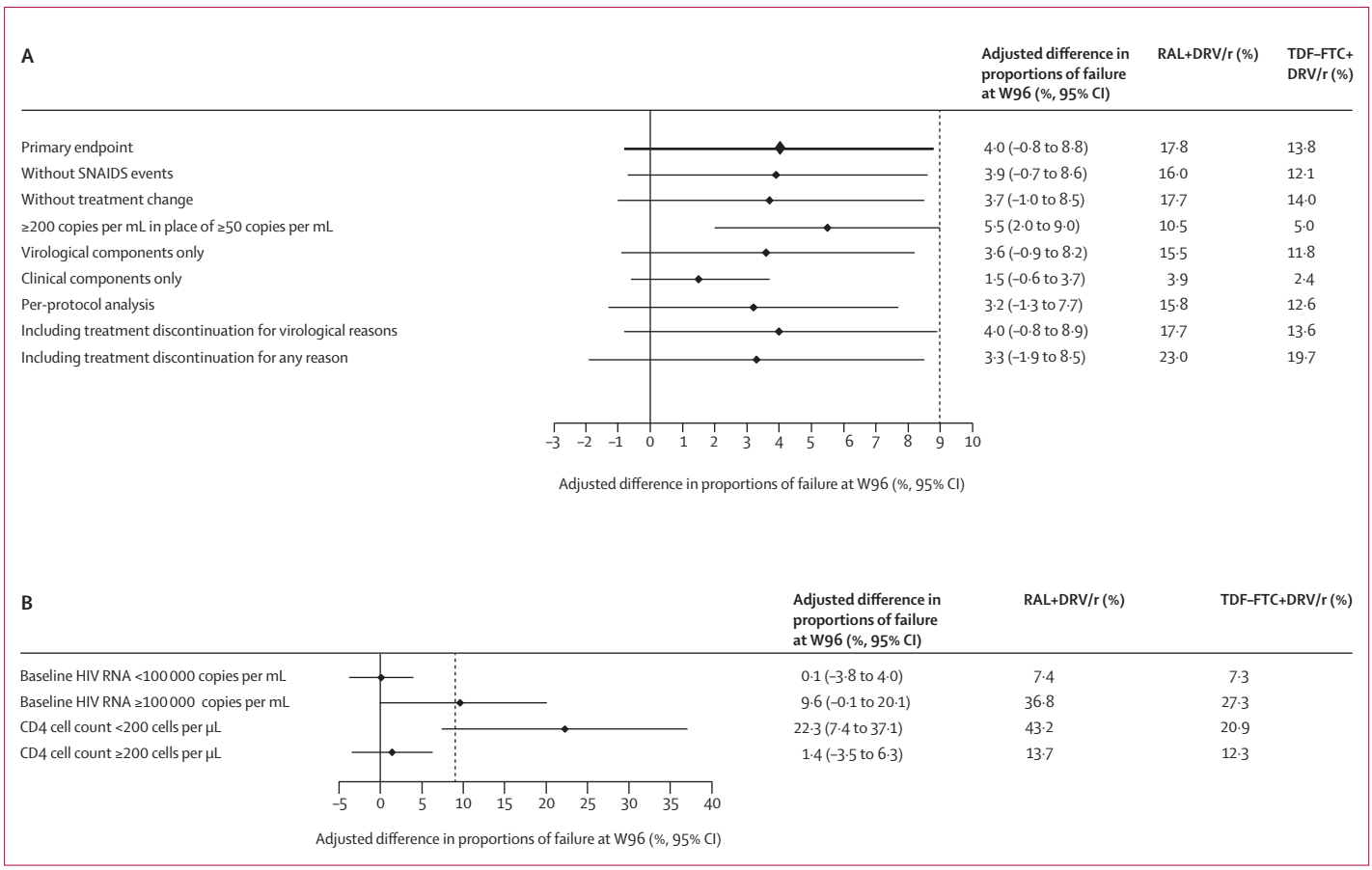

Figure 3: **Kaplan-Meier estimates of proportion of patients in each group reaching endpoints at week 96**
(A) Primary, sensitivity, and secondary analyses around the primary endpoint. (B) Analyses by baseline HIV-1 RNA concentration and CD4 cell count. W96=week 96. RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine. SNAIDS=serious non-AIDS event.

primary endpoint (table 2). At week 96, the Kaplan-Meier estimated proportions of treatment failure in the primary intention-to-treat analysis were 17·8% in the NtRTI-sparing group and 13·8% in the standard group (figure 2). The adjusted difference in treatment failure rate between groups was 4·0% (95% CI –0·8 to 8·8), which met the non-inferiority criterion. The HR for meeting the primary endpoint with the NtRTI-sparing regimen during all follow-up was 1·34 (95% CI 0·96–1·88). Sensitivity and secondary analyses supported non-inferiority (figure 3).

In the per-protocol analysis, the estimated treatment failure at 96 weeks was 15·8% for the NtRTI-sparing regimen and 12·6% for the standard regimen, and the adjusted difference in treatment failure rate between groups was 3·2% (95% CI –1·3 to 7·7; figure 3). The numbers of patients at risk of treatment failure at week 96 were 286 in the NtRTI-sparing group and 311 in the standard regimen group. The HR for the primary endpoint in the per-protocol analysis during all follow-up was 1·30 (95% CI 0·91–1·87).

Subgroup analyses showed that the NtRTI-sparing regimen was inferior to the standard regimen in patients with baseline CD4 cell counts of less than 200 cells per µL (figure 3). The interaction test for the Kaplan-Meier estimated treatment difference at week 96 in patients with CD4 counts of less than 200 cells per µL versus in those with 200 cells per µL or higher was significant (interaction test, p=0·010). A non-significant difference towards more failures in the NtRTI-sparing group was also seen in patients with HIV-1 RNA concentrations in plasma of 100 000 copies per mL or higher at baseline (interaction test, p=0·10). An exploratory post-hoc analysis that combined the effects of CD4 cell count and viral load at baseline indicated that the inferiority of the NtRTI-sparing regimen was restricted to patients with baseline CD4 cell counts of less than 200 cells per µL and HIV-1 RNA concentrations higher than 100 000 copies per mL (table 3). CD4 cell counts increased from baseline to week 96 in both treatment groups, by a mean of 268 cells per µL (95% CI 250–284) in the NtRTI-sparing group and 266 cells per µL (250–283) in the standard group (p=0·929). Mean change from baseline at week 96 for CD4 percentage was 11·0% (95% CI 10·3–11·6) in the NtRTI-sparing group and 12·1% (11·5–12·7) in the standard group (p=0·013). The estimated proportions of participants whose CD4 cell counts increased to more

	Baseline CD4 cell count <200 cells per µL and HIV RNA concentration <100 000 copies per mL (n=46)		Baseline CD4 cell count ≥200 cells per µL and HIV RNA concentration <100 000 copies per mL (n=484)		Baseline CD4 cell count <200 cells per µL and HIV RNA concentration ≥100 000 copies per mL (n=77)		Baseline CD4 cell count ≥200 cells per µL and HIV RNA concentration ≥100 000 copies per mL (n=198)	
	RAL+DRV/r	TDF–FTC+DRV/r	RAL+DRV/r	TDF–FTC+DRV/r	RAL+DRV/r	TDF–FTC+DRV/r	RAL+DRV/r	TDF–FTC+DRV/r
Number meeting endpoint	3/23	3/23	19/232	21/252	23/37	12/40	32/109	25/89
Proportion meeting primary endpoint	9·4%	9·0%	7·1%	7·1%	60·1%	29·9%	26·5%	28·4%
Difference (95% CI)	0·4% (–13·7 to 14·6)*	..	0% (–3·9 to 3·9)	..	30·3% (13·8 to 46·8)	..	–1·9% (–13·9 to 10·0)	..

RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine. *Difference unadjusted because of very small numbers in this group.

***Table 3*: Kaplan-Meier estimates of proportions of patients meeting primary endpoint at week 96**

than 500 cells per µL during follow-up were 84% and 82%, respectively. Time from randomisation to reach counts higher than this threshold was significantly shorter in the NtRTI-sparing group than in the standard group (median 17 weeks [IQR 5–64] *vs* 24 weeks [8–91]; log-rank p=0·042).

At week 96, the proportions of patients with fewer than 50 copies per mL of HIV-1 RNA in plasma and fewer than 200 copies per mL of HIV-1 RNA in plasma in the two groups are shown in figure 4. Estimated proportions of patients without loss of virological response were 87·6% in the NtRTI-sparing and 89·7% in the standard group at week 48 (adjusted difference 2·2%, 95% CI –0·9 to 5·3) and 78·6% and 82·2% at week 96 (3·6%, –1·5 to 8·6; log-rank p=0·158).

Among patients who underwent genotype testing to assess emerging resistance at the time of virological failure, treatment-emergent resistance was seen in no patients in the standard group and in six (21%) of 29 in the NtRTI-sparing group, five of whom had resistance to integrase and one to NtRTI (table 4). Among those with the major integrase resistance mutations, four had baseline HIV-1 RNA concentrations in plasma higher than 500 000 copies/mL and one of 146 445 copies/mL (appendix p 1).

Discontinuation of the randomised regimen for any reason was significantly higher for the NtRTI-sparing regimen than for the standard regimen (14·8% *vs* 9·1%, adjusted difference 5·8%, 95% CI 2·0 to 10·0) but more patients discontinued after reaching the primary endpoint in the NtRTI-sparing group (36 [44%] *vs* eight [16%]). Permanent discontinuation because of a treatment-limiting adverse event was similar in the two groups (1·5% *vs* 2·6%, adjusted difference –1·2%, 95% CI –3·1 to 0·7). During follow-up, safety outcomes in the two treatment groups were similar. Rates of adverse events leading to treatment modification were low for all grades (34 adverse events, 3·9 per 100 patient-years in the NtRTI-sparing group *vs* 38, 4·2 per 100 patient-years in the standard group) and also did not differ between groups for treatment-modifying grade 3–4 events (appendix p 2). Rates of serious adverse events were also similar in the two groups (89 events in 73 patients, 10·2 per 100 patient-years *vs* 75 events in 61 patients, 8·3 per 100 patient-years, p=0·198). Five patients died: four in the NtRTI-sparing group (one from each of melanoma, suicide, Burkitt's

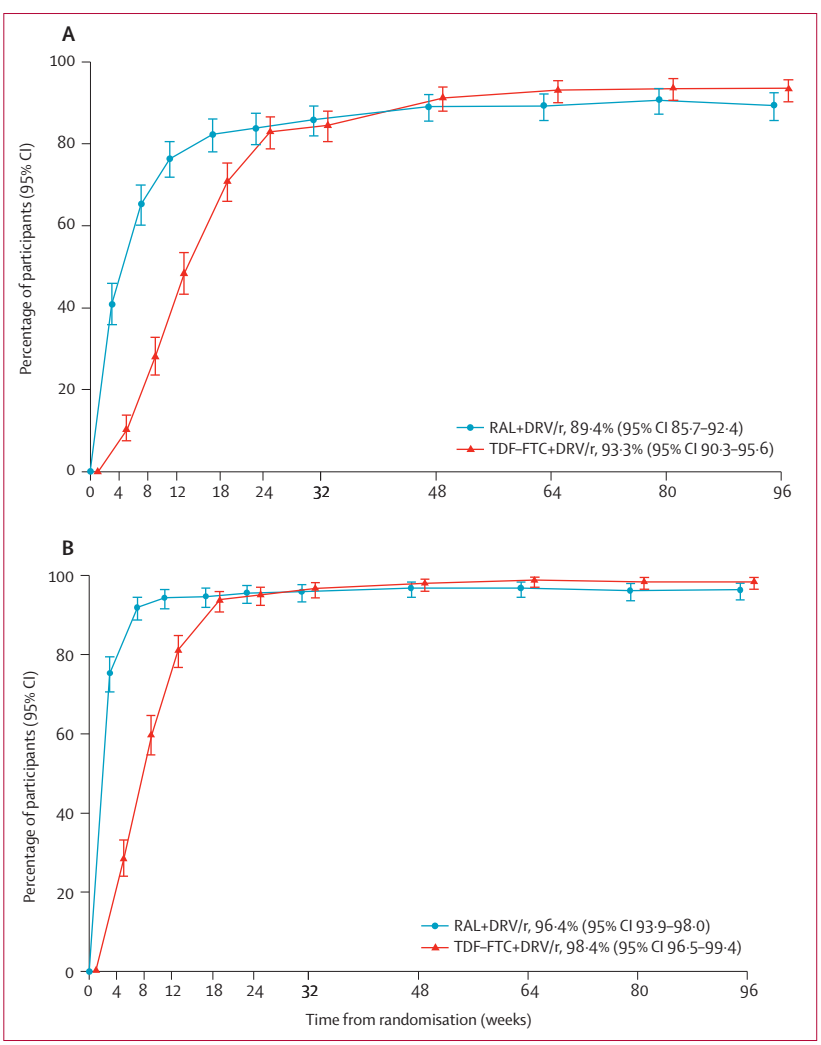

***Figure 4*: Virological response, by treatment group**
Data are proportion (95% CI), based on available viral load data. (A) Patients with HIV-1 RNA concentrations lower than 50 copies per mL. (B) Patients with HIV-1 RNA concentrations lower than 200 copies per mL. RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine.

	RAL+DRV/r (n=401)	TDF–FTC+ DRV/r (n=404)
All PDVF	66	52
Total number of patients who met criteria for genotype testing*	36	15
PDVF patients meeting criteria for genotype testing	33	9
No PDVF patients meeting criteria for genotype testing	3	6
Patients undergoing genotyping	29	13
Major resistance mutations	6	0
Reverse transcriptase	1†	0
Protease	0	0
Integrase	5‡	0

RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF–FTC=tenofovir–emtricitabine. PDVF=protocol-defined virological failure. *Genotypic testing carried out by local laboratories when patients had a single viral load >500 copies/mL at or after week 32 up to the end of follow up. †Lys65Arg mutation. ‡Asn155His mutation.

Table 4: **Virological failure and emerging resistance mutations per trial arm**

lymphoma, and severe sepsis with organ failure after drug rash with eosinophilia and systemic symptoms; the latter was deemed possibly related to study treatment) and one in the standard group (morphine overdose). Grade 2–4 rash was seen in 11 patients (1·3 per 100 patient-years) with the NtRTI-sparing regimen and in 14 patients (1·6 per 100 patient-years) with the standard regimen (p=0·610). Three and six of these patients, respectively, discontinued randomised treatment but did not leave the trial. No patients had grade 4 rash. Immune reconstitution syndrome events were confirmed in two patients in the NtRTI-sparing group and one in the standard group.

Concentrations of fasting total cholesterol, HDL cholesterol, and LDL cholesterol in serum increased over time in the two treatment groups, with mean increases by week 96 being significantly higher in the NtRTI-sparing than in the standard group (total cholesterol 0·9 *vs* 0·5 mmol/L, p<0·001; HDL cholesterol 0·2 *vs* 0·1 mmol/L, p<0·001; and LDL cholesterol 0·5 *vs* 0·4 mmol/L, p=0·021). By week 96, no difference was seen between groups in the mean changes in the ratio of total cholesterol to HDL cholesterol or of triglyceride concentrations. Estimated creatinine clearance from baseline at week 96 was increased by a mean of 0·8 mL/min in the NtRTI-sparing group and decreased by a mean of –4·6 mL/min in the standard group (p<0·001). No patient in either group had grade 2 or higher increases in creatinine concentration. The numbers of patients with grade 3 or 4 treatment-emergent increases in creatine phosphokinase concentration were 24 (6%) in the NtRTI-sparing group and 20 (5%) in the standard group, and of grade 3–4 increases in alanine aminotransferase concentrations were 12 (3%) and four (1%; p=0·036).

Discussion

NEAT001/ANRS143 was a fully powered phase 3 trial of an innovative NtRTI-sparing treatment regimen that uses an integrase strand-transfer inhibitor and a ritonavir-boosted protease inhibitor, compared with an NtRTI-based standard regimen, as first-line antiretroviral therapy. The NtRTI-sparing regimen was well tolerated and exhibited non-inferior efficacy. Non-inferiority was supported by sensitivity and secondary analyses, including a per-protocol analysis. When extending causes of treatment failure by including treatment discontinuation for any reason along with the components of the clinical and virological endpoint, we found that non-inferiority was maintained. This finding is highly relevant as it reflects clinical practice. The week 96 virological response rates for patients who received either of the study regimens were consistent with those shown with 400 mg raltegravir twice daily or 800 mg darunavir and 100 mg ritonavir once daily in combination with tenofovir–emtricitabine in previous studies of treatment-naive adults with HIV-1.[7,15] In the ARTEMIS trial,[15] 79% of patients receiving ritonavir-boosted darunavir plus tenofovir–emtricitabine had a confirmed viral load of less than 50 copies per mL at week 96, and in our study the proportion was 82%.

Previous studies of NtRTI-sparing regimens, in which non-nucleoside reverse transcriptase inhibitors were combined with ritonavir-boosted protease inhibitors as alternative first-line antiretroviral therapy, showed no compelling evidence of benefit over standard regimens.[16,17] Only a few studies have previously explored first-line NtRTI-sparing regimens comprising a ritonavir-boosted protease inhibitor plus an integrase strand-transfer inhibitor (panel). A pilot randomised trial showed similar efficacy and safety for an NtRTI-sparing regimen of raltegravir plus ritonavir-boosted lopinavir and a traditional three-drug regimen of tenofovir–emtricitabine plus ritonavir-boosted lopinavir.[18] That study, however, included 206 participants and had a large non-inferiority margin of –20%.[21] In a phase 2, single-arm, open-label study of 800 mg darunavir and 100 mg ritonavir once daily plus 400 mg raltegravir twice daily in antiretroviral-naive patients, a 26% virological failure rate was seen after 48 weeks.[22] As expected, patients with high viral load at baseline were at increased risk of virological failure and treatment-emergent integrase resistance, but the absence of a control group limits the interpretation of these results.

Prespecified subgroup analyses in our study showed that our NtRTI-sparing regimen was inferior to the standard regimen in patients with baseline CD4 cell counts lower than 200 cells per µL, but non-inferior efficacy was found in patients with baseline CD4 cell counts higher than 200 cells per µL. The latter subgroup included 85% of our study population and probably reflects a large portion of the current target population for first-line treatment because guidelines recommend early diagnosis of HIV infection and starting

antiretroviral therapy to maximise treatment success and prevention of transmission.[23–25] Of note, there was no signal for a difference in failure rates between the two treatment groups for patients with baseline CD4 cell counts lower than 200 cells per µL and HIV-1 RNA concentrations lower than 100 000 copies per mL and for those with baseline CD4 cell counts higher than 200 cells per µL. We suggest, therefore, that raltegravir plus ritonavir-boosted darunavir should be avoided as first-line therapy in patients with CD4 cells counts lower than 200 cells per µL.

In the NtRTI-sparing group in our trial, the frequency of emerging resistance mutations was higher than in the standard regimen group. However, with only six documented cases among 401 patients over a median of 123 weeks of follow-up, the number of patients with such mutations was small. By contrast, in the phase 3 ACTG 5142 trial[17] 39 (16%) of 250 patients receiving efavirenz plus ritonavir-boosted lopinavir acquired resistance mutations during a median follow-up of 112 weeks. The consequence of developing resistance in our study was limited, as five of the six patients had mutations that confer resistance only to integrase strand-transfer inhibitors and, therefore, the virus was still fully susceptible to NtRTIs and protease inhibitors. Furthermore, in these five cases, the emerging resistance mutation was Asn155His, which is one of the key pathways to resistance to raltegravir but which does not lead to cross-resistance to the newer integrase strand-transfer inhibitor dolutegravir.[26] Of note, all five patients who acquired emerging integrase resistance mutations had HIV-RNA concentrations higher than 100 000 copies per mL at baseline.

Time to reach CD4 cell counts higher than 500 cells per µL was shorter in the NtRTI-sparing group than in the standard group, but whether this difference is clinically relevant is unknown. Cohort studies have shown that in individuals with HIV who attained a long-term CD4 cell count of at least 500 cells per µL with treatment, mortality rates were similar to those in the general population.[27]

Discontinuation of treatment due to adverse events was low and the rates were similar in the two groups. This finding supports the overall good tolerability of antiretroviral therapy and in particular the good safety profile of the two regimens used in this trial. Likewise, in studies of integrase strand-transfer inhibitors, rates of discontinuation because of adverse events during 96 weeks ranged from 2·4% to 4·9%.[28,29] The fasting lipid laboratory results favoured the standard regimen in our study, whereas changes in estimated glomerular filtration rate favoured the NtRTI-sparing regimen.

The generalisability of our findings might be limited by the fact that few women were enrolled and that most of the participants had CD4 cell counts between 200 and 500 cells per µL at baseline. Lack of blinding is usually deemed to be a limitation in randomised clinical trials. Blinding in this trial would have increased the pill burden, which is a potential risk factor for decreased adherence to treatment and might have limited external validity of the results in practice conditions.[30] As pill

Panel: Research in context

Systematic review

We searched PubMed with the keywords "antiretroviral therapy", "clinical trial", "HIV integrase inhibitor", "HIV protease inhibitor", and "reverse transcriptase inhibitor" for papers published in English between Jan 1, 2006, and April 1, 2014. Antiretroviral therapy is now recommended for all patients with HIV infection to reduce the risk of disease progression and prevent transmission. Recommended standard therapy is with two nucleoside or nucleotide analogue reverse transcriptase inhibitors (NtRTIs) plus either a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, or an integrase strand-transfer inhibitor, but tenofovir–emtricitabine, the most frequently used NtRTI, is associated with renal and bone complications.[2–4] HIV requires lifelong treatment and, therefore, emphasis is put on identifying first-line regimens that combine optimum efficacy with long-term safety. Several antiretrovirals have been authorised for use in first-line regimens on the basis of 48 week data. Data from studies of longer-term follow-up periods are useful because they show whether regimens are sustainable, convenient, and free from new emerging side-effects. Week 96 results of randomised trials of NtRTI-sparing dual therapy with ritonavir-boosted lopinavir and a second agent, such as efavirenz or raltegravir, compared with standard first-line triple therapy have been reported. Dual therapy had sustainable antiviral efficacy similar to the standard regimens, but occurrence of drug resistance at the time of virological failure was more frequent and tolerability of ritonavir-boosted lopinavir or efavirenz was poorer than with the standard regimens.[17,18] The combination of atazanavir plus raltegravir achieved virological suppression rates similar to the standard combination of tenofovir–emtricitabine plus ritonavir-boosted atazanavir in treatment-naive patients, but resistance developed to raltegravir and higher rates of hyperbilirubinaemia were seen with twice-daily atazanavir compared with once-daily ritonavir-boosted atazanavir.[19] On the basis of these findings, further clinical development of dual therapy with atazanavir plus raltegravir was halted. In combination with two nucleoside analogues, raltegravir was well tolerated with a greater rate of virological success after 5 years than that achieved with efavirenz in first-line therapy.[20] We did a 96 week trial of the NtRTI-sparing regimen of raltegravir and ritonavir-boosted darunavir.

Interpretation

We did a phase 3 open-label non-inferiority design to compare this NtRTI-sparing regimen with the standard regimen of fixed-dose tenofovir–emtricitabine plus ritonavir-boosted darunavir. Overall, the NtRTI-sparing strategy was well tolerated and had similar efficacy to the standard regimen at 96 weeks. Prespecified subgroup analyses showed that the NtRTI-sparing strategy was less efficacious than the standard regimen in patients with CD4 cell counts lower than 200 cells per µL at baseline. Despite a low rate of virological failure in the two treatment groups, emergence of resistance mutations was increased in the raltegravir group. Overall, though, our findings suggest that the NtRTI-sparing regimen of raltegravir and ritonavir-boosted darunavir was non-inferior to standard therapy and represents an alternative option for first-line therapy in patients with CD4 cell counts higher than 200 cells per µL. Future randomised trials of NtRTI-sparing regimens should explore new combinations, such as ritonavir-boosted darunavir plus dolutegravir, or an integrase inhibitor plus a new non-nucleoside reverse transcriptase inhibitor. The latter combination could, theoretically, notably improve tolerability. Such new combinations might be especially important to investigate in the context of an ageing HIV population.

burden is an important consideration in modern antiretroviral therapy, we chose an open-label design to allow both regimens to be administered as in real clinical practice.[31] In terms of internal validity, the only component of the primary endpoint that might have been subjective to some degree was insufficient virological response by week 18, but sensitivity analysis of this feature, irrespective of treatment change, showed the results to be robust. All other virological components were assessed by testing in laboratories, in which the staff were unaware of treatment assignment.

A strength of this trial is that the composite primary endpoint is of direct clinical relevance because it combines virological and clinical components.[32] The clinical components were reviewed by the endpoint review committee, whose members were unaware of treatment allocations. Another strength of our design is the non-inferiority margin of 9%, which compares with margins of 10–12% in other trials.[33] Thus, although the upper bound of the two-sided 95% CI for the difference in the proportion of participants reaching the primary endpoint was only just below the 9% margin, the results are still conservative compared with those in other non-inferiority trials of antiretrovirals.

In conclusion, the NtRTI-sparing regimen of raltegravir plus ritonavir-boosted darunavir was well tolerated and was non-inferior to standard treatment with tenofovir–emtricitabine plus ritonavir-boosted darunavir in treatment-naive patients with CD4 cell counts higher than 200 cells per μL.

Contributors

FR, AGB, LR, AA, JRA, CA, SV, GC, and AP designed the study in consultation with the trial development team. FR, J-MM, AA, JRA, CA, J-FD, and AP enrolled participants into the study. LR, JG, FH, CS, JS, CW, POJ, RVL, and GC contributed to the coordination and oversight of the study. AGB and ECG did the statistical analysis. All authors participated in data interpretation. The manuscript was drafted by FR, LR, ECG, CA, and AP. All authors provided input to the report and approved the final version of the manuscript.

Declaration of interests

FR and J-MM have received honoraria for being an adviser or invited speaker at conferences and have received research grants from Abbvie Labs, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Laboratories, MSD, Tobira, and ViiV Healthcare. The institution of LR, CS, CW, and GC has received support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen Pharmaceuticals, MSD, Pfizer, Roche, Tibotec, and ViiV Healthcare for the organisation of an annual academic workshop and for ongoing clinical trials of Inserm-ANRS. JRA has received advisory fees, speaker fees, and grant support from Janssen Pharmaceuticals, Abbvie, Bristol-Myers Squibb, Gilead, Janssen Pharmaceuticals, MSD, Tibotec, Tobira, and Viiv Healthcare. AA has received honoraria for consultancy or research grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Laboratories, and ViiV Healthcare. CA is a board member of and has received travel grants from Gilead Sciences, Janssen Pharmaceuticals, Merck Laboratories, and ViiV Healthcare. SV is a member of scientific advisory boards of Gilead Sciences, Merck Laboratories, and ViiV Healthcare. AP has been an adviser and invited speaker for and received honoraria, research grants, and travel and education grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Merck Laboratories, Tobira, and ViiV Healthcare. The other authors declare no competing interests.

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Further investigators

See appendix pp 3–5 for the trial management team, other study investigators, the endpoint review committee, and the substudy working groups.

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